Author's response to reviews

Title: Demographic determinants and effect of pre-operative angiotensin converting enzyme inhibitors and angiotensin receptor blockers on the occurrence of atrial fibrillation after CABG surgery.

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Demographic determinants and effect of pre-operative angiotensin converting enzyme inhibitors and angiotensin receptor blockers on the occurrence of atrial fibrillation after CABG surgery.

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Abstract

Background

Atrial fibrillation (AF) occurs in about 27% to 40% of post cardiac surgery patients. AF following CABG surgery is associated with a two-fold increase in morbidity and mortality. Various demographic risk factors and medications have been studied to predict the occurrence of this arrhythmia. The role of angiotensin related medications on the occurrence of AF in CABG patients is not determined.

Methods

Retrospective clinical and statistical analysis was made of all the patients who had undergone CABG surgery at Lehigh Valley Hospital during the years 2005 and 2006. Patients with chronic AF and those undergoing valvular surgery with CABG were excluded. Statistic analysis included chi-square test for categorical and student t-test for continuous variables.

Results

757 patients (560 males and 197 females) were studied. AF occurred in 19% of the patients. Age (70.5 vs. 65.1, p <0.005) and presence of hypertension (OR: 1.92, 95%CI: 1.086-3.140, p= 0.025) were significantly associated with occurrence of AF. Though statistically not significant, patients on ARBs had fewer events (OR: 0.78, 95%CI: 0.431-1.410, p = 0.41) while those on ACE inhibitors (OR: 1.01, 95%CI: 0.753-1.608, p = 0.63) and beta-blockers (OR: 1.172, 95%CI: 0.734-1.870, p = 0.56) had more events of post-surgical AF.

Conclusions

Advanced age and presence of hypertension were independent predictors of post-CABG
AF. ARBs unlike ACE inhibitors and beta-blockers reduced the occurrence of post-surgical AF, though this was not statistically significant. Further studies are needed to better delineate the role of angiotensin related medications on reduction of post-surgical AF.
Background

Atrial fibrillation (AF) occurs in about 27% to 40% of post cardiac surgery patients (1). The presence of this arrhythmia following coronary artery bypass graft surgery (CABG) is associated with a two-fold increase in cardiovascular morbidity and mortality (2). There is an association of post operative AF with a higher occurrence of heart failure and cerebral ischemic accidents, both resulting in longer hospital stay, and consequently in higher surgery costs (3-6). The etiology of postoperative AF is not well defined, although recent studies suggest that a multi-factorial mechanism is involved, which includes oxidative stress, inflammation, atrial fibrosis, excessive production of catecholamines, changes in autonomic tone and in the expression of connexins (7-11). Multiple investigations have been performed to identify the demographic risk factors, association of medications and the predictors of post operative AF, but there is no conclusive information (12). Epidemiological studies in non-surgical patients have shown that the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) have an overall effect of 18% risk reduction in new-onset AF across the trials, and 43% risk reduction in patients with heart failure (13). The present study was aimed at identifying the preoperative demographic predictors and the effects of ACEI and ARBs on the occurrence of AF in patients who underwent CABG surgery.

Methods

A retrospective evaluation of patients who have undergone CABG surgery at Lehigh Valley Hospital was done. Patients were identified by ICD-9 surgical code for coronary artery bypass grafting, recorded as admitted between January 2005 and December 2006. Each chart was reviewed and data entered by the investigators NS and MQM.
Postoperative AF was defined as an entry into the case report form or by detection on the postoperative electrocardiogram. Details of medications received in the pre-operative period were noted. Included cases were divided into three groups: those on ACEI, those on ARBs and those on neither of these medications. Consecutive patients undergoing coronary arterial bypass surgery between January 2005 and December 2006 were included in the study. Patients younger than 18 years, those who were undergoing valvular surgery in addition to the CABG and patients with known AF at the time of going for the surgery were excluded from the study. Prior medical illness including hypertension and diabetes mellitus were studied as possible contributing causes of post surgical AF. The institutional review board at Lehigh Valley Hospital granted ethical approval for this study.

**Sample size and statistical analysis**

Primary goal of the proposed study was to test the null hypothesis that the proportion positive for AF were identical in those taking either ARBs or ACEI and those not on these medications before CABG surgery. This was done using a two-tailed t-test with the criterion for significance (p) set at 0.05. In the absence of identical studies, assumptions of effect size were based on a similar study that suggested a -0.20 reduction effect of prophylactic use of beta-blockers against AF in surgical patients. A smaller relative risk reduction of -0.15 was also considered. Assuming the difference in proportions of -0.20 (specifically 0.32 versus 0.12), a proposed sample size of 70 for each of the two groups will have a power of 82.2% to yield a statistically significant result. Assuming the difference in proportions of -0.15 (specifically 0.32 versus 0.17), a proposed total sample size of 240 will have power of 77.4% to yield a statistically significant result.
Statistical analysis was conducted using SPSS 15.0 software. Group comparisons were performed using chi-square, t-test, ANOVA and non-parametric Kruskal-Wallace tests where appropriate. For those measures showing significant differences, appropriate odds ratios and 95% confidence intervals were calculated to provide ease of interpretation.

**Results**

757 patients fulfilled the criteria and were included in the study. All the patients had on-pump CABG surgery. There were 560 males and 197 females. The mean age of the patients was 66.1 years with SD of 10.9 years. The average left ventricular ejection fraction (LVEF) was 51.2%. The duration of hospital stay ranged from 1 day to 45 days (mean 7.5 days with SD of 4.5 days). 634 (83%) patients were known to have hypertension, 606 were on beta-blockers, 144 on ACEI, and 94 were on ARBs. There were 262 (35%) patients with diabetes mellitus. 476 (63%) patients had history of smoking. 149 (20%) had COPD at the time of the surgery. Post operative AF occurred in 144 (19%) of the patients.

**Comparison of patients with and without AF following the CABG**

Patients with AF following the CABG were noted to be older than those without the event, which was statistically significant (70.5 +/- 8.1 years vs. 65.1 +/- 11.2 years, p<0.001). Patients with AF had a significantly longer hospital stay (9.5 +/- 5.4 days vs. 6.9 +/- 4.3 days, p=0.001). The occurrence of AF was not different in males as compared to females. There was no association of the arrhythmia with either smoking or history of COPD (Table 1). There was a significantly higher incidence of AF in hypertensive patients (OR: 1.92, 95%CI: 1.086-3.140, p= 0.025), but it was noted that on matching for age, this effect was lost. On subgroup analysis of hypertensive patients there was no
association of occurrence of AF with the variables studied except as mentioned for age. Patients with diabetes mellitus had a higher incidence, while patients on ARBs had a lower incidence of AF, though neither were statistically significant. ACEI and beta-blockers had no effect on post-surgical AF, so was the case with Aspirin and Clopidogrel (Table 1).

Subgroup analysis of diabetic patients

On subgroup analysis of diabetic patients (Table 2), there was no association of AF with gender, smoking, or COPD. Again there was a noted higher incidence in hypertensive patients (p=0.04). There was noted reduction in the occurrence of AF in patients who were on beta-blockers (p=0.78) and ARBs (p=0.45). It was also noted that there was fewer events patients on aspirin (p=0.13).

Subgroup analysis of patients who are older than 65 years with hypertension and diabetes

On statistic analysing of this subgroup of patients we noted that Aspirin, Clopidogrel, beta-blockers reduced post operative AF, though this was not statistically significant (Table 3). Patients on ARBs had an odds ratio of 0.44 (p=0.11) in reduction of AF occurrence while those on ACEI had an odds ratio of 1.01 (p=0.99).

Discussion

AF is a common cardiac arrhythmia following cardiothoracic surgery. AF occurs in about 27% to 40% of post cardiac surgery patients (1). AF most frequently occurs in the first 2 to 3 days after cardiothoracic surgery (14). The presence of this arrhythmia following coronary artery bypass graft surgery is associated with a two-fold increase in cardiovascular morbidity and mortality (2). There have been various studies noting the positive effects of ACEI and ARBs on the occurrence of this complication, though it is
In our retrospective study, we looked at patients who underwent CABG without valvular surgery, on the contributing factors and effects of various cardiac medications on the occurrence of post surgical AF. In our analysis AF occurred in 19% of patients. The reduced incidence of AF amongst our patients as compared to other quoted studies (1, 15, 16) is possibly attributed to the exclusion of patients who were also undergoing valvular surgery, which is known to increase the incidence of the AF. Increasing age was noted to be associated with higher occurrence of AF, whereas gender, diabetes, and left ventricular ejection fraction were not associated with AF. Patients with AF had a significantly longer hospital stay (9.5 +/- 5.4 days vs. 6.9 +/- 4.3 days, p=0.001).

The noted influence of age as the positive predictor of occurrence of AF has been noted previously (17). We did see a higher occurrence of AF among patients with hypertension, but it was noted that on matching to age, this effect was lost. This finding reaffirming the role of age was unique to our study.

Use of ACEI and ARBs as a medication to reduce AF following CABG is controversial. The explanation for the increased occurrence of AF in post-operative patients on ACEI and ARBs is thought to be attributed to the higher prevalence of hypertension and left ventricular hypertrophy in these patients (15). At the same time angiotensin blockers have been reported not only to prevent left atrial dilation and atrial fibrosis but also to slow conduction velocity in the heart, explaining the reduction of AF in post CABG patients (18-20). In our study we compared the effects of ACEI and ARBs as separate groups on the occurrence of AF; this has not been done previously. Interestingly we noted that while patients on ARBs had fewer occurrences of AF post operatively; this
was not the case in patients who were on ACEI. Similar differences have been noted
between the two medications in relation to reduction of cerebro-vascular accidents (21).
The likely explanation for this finding is not known, though there are a few hypothetical
explanations for its occurrence. ACEI antagonize the effects of AT-1 and AT-2 receptors
while ARBs block the AT-1 and stimulate AT-2 receptors. Stimulation of AT-2 receptors
counteracts some effects of AT-1 receptors and may have antiproliferative and
 cardioprotective action. In addition the ACEI do not affect angiotensin II production via
non-ACE pathways, whereas ARBs antagonize all effects consequent upon AT-1
receptor activation. Chymase activity (non-ACE pathway) is present in the human heart
tissue extract and is higher in the left atrium than in other chambers (22). In a recent
study, treatment with Valsartan was not associated with a reduction in the incidence of
recurrent AF (23). This study enrolled patients who were in sinus rhythm but had
previous documented episodes of AF and they looked at the incidence of reoccurrence of
the arrhythmia. Half of the studied patients were on other antiarrhythmic medications like
amiodarone, sotalol and class I antiarrhythmic agents, which was quite in contrast to our
study population. Though there was only a marginal reduction of occurrence of AF in the
treated population in that study, we could speculate that there could have been a bigger
benefit in medication naive patients. It is also well established that the etiology of AF
following CABG is very different from non-surgical patients who were studied in the
GISSI-AF trial.

Our study had some limitations; firstly, we were not able to assess left atrial size and left
ventricular hypertrophy which are known risk factors of post operative AF, and would
recommend that this data be included in further studies. Secondly, as this was a cohort
study, investigators did not dictate the use of ACEI or ARB or its dosages, nor had any control on the duration of medications. This lack of randomisation in observational studies could introduce both confounding factors and biases. We addressed most of the confirmed risk factors by matching patients in our statistical analysis.

**Conclusion**

Advanced age and presence of hypertension were independent predictors of post-CABG AF. ARBs unlike ACE inhibitors and beta-blockers reduced the occurrence of post-surgical AF, though this was not statistically significant. Further studies are needed to better delineate the role of angiotensin related medications on reduction of post-surgical AF.

**Competing interests**

The authors declare that they have no financial or non-financial competing interests.

**Authors' contributions**

NS was involved with design of the study, collecting the data, coordination and drafting the manuscript. MQM was involved in collection of the data and drafting the manuscript. SE participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.
References:


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Table 1: Comparison of discrete variables between patients who developed AF following CABG with those who did not have the arrhythmia following the surgery (Chi-squares test)

<table>
<thead>
<tr>
<th>Particulars (patients in the group)</th>
<th>AF positive (n=144)</th>
<th>AF negative (n=613)</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (558)</td>
<td>107</td>
<td>456</td>
<td>0.97</td>
<td>0.89</td>
</tr>
<tr>
<td>Smoker (476)</td>
<td>86</td>
<td>390</td>
<td>0.87</td>
<td>0.45</td>
</tr>
<tr>
<td>COPD (149)</td>
<td>25</td>
<td>124</td>
<td>0.84</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension (634)</td>
<td>129</td>
<td>505</td>
<td>1.92</td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetes (262)</td>
<td>56</td>
<td>206</td>
<td>1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Aspirin (693)</td>
<td>133</td>
<td>560</td>
<td>1.16</td>
<td>0.66</td>
</tr>
<tr>
<td>Clopidogrel (261)</td>
<td>56</td>
<td>205</td>
<td>1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Betablockers (606)</td>
<td>118</td>
<td>488</td>
<td>1.17</td>
<td>0.51</td>
</tr>
<tr>
<td>ACEI (144)</td>
<td>84</td>
<td>60</td>
<td>1.01</td>
<td>0.75</td>
</tr>
<tr>
<td>ARB (94)</td>
<td>15</td>
<td>79</td>
<td>0.78</td>
<td>0.41</td>
</tr>
<tr>
<td>Statins (557)</td>
<td>107</td>
<td>450</td>
<td>1.28</td>
<td>0.71</td>
</tr>
<tr>
<td>Sternal infections (1)</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>0.38</td>
</tr>
<tr>
<td>Prolonged ventilation (27)</td>
<td>10</td>
<td>17</td>
<td>2.64</td>
<td>0.01</td>
</tr>
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</table>
Table 2a: Comparison amongst diabetic patients of various factors that could contribute to post operative AF (n=262).

<table>
<thead>
<tr>
<th>Particulars (patients in the group)</th>
<th>AF positive (n = 56)</th>
<th>AF negative (n=206)</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (184)</td>
<td>38</td>
<td>146</td>
<td>1.15</td>
<td>0.66</td>
</tr>
<tr>
<td>Smokers (147)</td>
<td>29</td>
<td>118</td>
<td>0.80</td>
<td>0.46</td>
</tr>
<tr>
<td>COPD (43)</td>
<td>5</td>
<td>38</td>
<td>0.43</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension (240)</td>
<td>55</td>
<td>185</td>
<td>6.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Aspirin (240)</td>
<td>49</td>
<td>191</td>
<td>0.47</td>
<td>0.13</td>
</tr>
<tr>
<td>Clopidogrel (90)</td>
<td>19</td>
<td>71</td>
<td>0.96</td>
<td>0.90</td>
</tr>
<tr>
<td>ARB (41)</td>
<td>7</td>
<td>34</td>
<td>0.71</td>
<td>0.45</td>
</tr>
<tr>
<td>ACEI (112)</td>
<td>26</td>
<td>86</td>
<td>1.19</td>
<td>0.57</td>
</tr>
<tr>
<td>Beta-blockers (212)</td>
<td>45</td>
<td>167</td>
<td>0.90</td>
<td>0.78</td>
</tr>
<tr>
<td>Statins (198)</td>
<td>44</td>
<td>154</td>
<td>1.57</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Table 2b: Comparison amongst diabetic patients of various factors that could contribute to post operative AF.

<table>
<thead>
<tr>
<th></th>
<th>AF positive</th>
<th></th>
<th>AF negative</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>71.2</td>
<td>8.6</td>
<td>66.3</td>
<td>10.8</td>
<td>0.002</td>
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<tr>
<td>SD</td>
<td>49.5</td>
<td>12.8</td>
<td>49.2</td>
<td>11.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Days</td>
<td>10.1</td>
<td>4.3</td>
<td>7.7</td>
<td>5.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table 3: Comparison of various factors amongst patients older than 65 years, positive history of hypertension, and diabetes for occurrence of post-operative AF (n=157).

<table>
<thead>
<tr>
<th>Particulars</th>
<th>AF positive (n = 56)</th>
<th>AF negative (n=206)</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (108)</td>
<td>29</td>
<td>79</td>
<td>0.98</td>
<td>0.97</td>
</tr>
<tr>
<td>Smokers (85)</td>
<td>20</td>
<td>65</td>
<td>0.70</td>
<td>0.32</td>
</tr>
<tr>
<td>Aspirin (143)</td>
<td>37</td>
<td>106</td>
<td>0.63</td>
<td>0.42</td>
</tr>
<tr>
<td>Clopidogrel (57)</td>
<td>13</td>
<td>44</td>
<td>0.72</td>
<td>0.40</td>
</tr>
<tr>
<td>ARB (32)</td>
<td>5</td>
<td>27</td>
<td>0.44</td>
<td>0.11</td>
</tr>
<tr>
<td>ACEI (71)</td>
<td>19</td>
<td>52</td>
<td>1.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Beta-blockers (131)</td>
<td>34</td>
<td>97</td>
<td>0.79</td>
<td>0.61</td>
</tr>
<tr>
<td>Statins (120)</td>
<td>33</td>
<td>87</td>
<td>1.70</td>
<td>0.50</td>
</tr>
</tbody>
</table>